Life-threatening pericardial bleed complicating atrial fibrillation ablation associated with edoxaban therapy successfully managed with prothrombin complex concentrate

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Introduction

The risk of pericardial bleeding complicating atrial fibrillation (AF) ablation is estimated to be around 0.5%–1%.[1] The consequences may be exacerbated by the need for anticoagulation for prophylaxis of thromboembolism. Once-daily administered direct oral anticoagulants (DOACs) such as edoxaban can be safely continued uninterrupted at the time of AF ablation.[2] However, management of bleeding complications in the context of DOAC therapy remains a challenge, especially as anti-factor Xa DOACs do not currently have licensed specific reversal agents. Dabigatran, a direct thrombin inhibitor, can be reversed using the agent idarucizumab, but reversal agents for other DOACs are still in development.[3]

Current guidelines only advocate the use of prothrombin complex concentrate (PCC) to reverse anticoagulation from vitamin K antagonists such as warfarin in the context of life-threatening bleeding or prior to emergency procedures.[4] On the other hand, the use of PCC in the context of DOAC therapy is not clearly supported by any current guidelines, although some suggest that it can be considered.

PCC is a pooled plasma product that contains the vitamin K–dependent blood clotting factors II, VII, IX, and X in concentrations around 25 times that of normal plasma.[5] Various forms of PCC exist including 4-factor PCC, which contains all the above pro-coagulants, and 3-factor PCC, which contains very little factor VII. Four-factor PCC is commonly used in the UK. PCC is usually ordered from the local hematology lab based on a patient's weight and degree of clotting dysfunction. It is quick to administer and can normalize vitamin K–dependent clotting within minutes. Alternative methods of restoring clotting function such as the use of fresh frozen plasma in comparison may take much longer to obtain, thaw, and administer, by which time further bleeding could have disastrous consequences.[5]

DOACs such as rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors. Dabigatran is a direct thrombin inhibitor.[6] Factor Xa inhibitors act 1 step earlier within the common pathway of the clotting cascade to convert prothrombin into thrombin. Thrombin then converts fibrinogen to fibrin, which, together with platelets, forms clot.[6] DOACs have a variable effect on vitamin K–dependent clotting pathways, making clotting assays such as the international normalized ratio an unreliable measure of anticoagulation in such context.[6] The effect of PCC on reversing anticoagulation from DOACs is less well understood and requires further study.

So far there is limited data regarding the efficacy of PCC to reverse anticoagulation from DOACs. No large randomized studies have been conducted. Here we report on the successful use of PCC in the management of a life-threatening pericardial bleed complicating AF ablation in the context of edoxaban therapy.

Case report

A 76-year-old man was admitted for an elective AF ablation under general anesthetic. He was diagnosed with persistent AF 2 years prior to this by his general practitioner. He also had moderate left ventricular dysfunction (ejection fraction 35%–40%) with calcific coronary arteries but no significant intracoronary disease, tablet-controlled type 2 diabetes, and chronic obstructive pulmonary disease. Electrical cardioversion was previously performed with restoration of sinus rhythm and symptomatic benefit and he was therefore listed for AF ablation. He had been on warfarin but was subsequently switched to edoxaban 60 mg once daily.

On the day of his ablation he remained in sinus bradycardia. The last dose of edoxaban was taken by the patient approximately 12 hours before the procedure. The planned strategy for AF ablation was pulmonary vein isolation using cryoablation. The procedure was performed under general

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KEY TEACHING POINTS

- Management of bleeding as a complication of atrial fibrillation ablation in the context of direct oral anticoagulant (DOAC) therapy can be challenging.
- Prothrombin complex concentrate (PCC) can be considered to reverse DOAC anticoagulation, but evidence is currently limited.
- This case suggests that PCC can be effective to reverse edoxaban anticoagulation in the event of severe bleeding.

anesthetic. Two 8 French sheaths and 1 7 French sheath were placed into the right femoral vein. A deflectable decapolar catheter was placed into the coronary sinus. Heparin boluses were used to keep the patient fully anticoagulated, keeping the activated coagulation time greater than 300 seconds. The first dose of heparin was 9000 units given before transseptal puncture. Transseptal puncture was performed under transesophageal echocardiographic, fluoroscopic, and pressure monitoring guidance, using a LAMP 90 sheath (St Jude Medical, Austin, TX) and BRK needle (St Jude Medical), successfully and without complication. The activated clotting time (ACT) was 317 seconds at 15 minutes and 308 seconds at 30 minutes.

Venograms of the pulmonary veins were being performed using the LAMP 90 sheath. Catheter manipulation towards the right pulmonary veins was reported to be extremely difficult and at this point dye staining was seen on fluoroscopy at the tip of the sheath at the atrial border. Echocardiography revealed a 1.6 cm pericardial effusion with early features of cardiac tamponade. Pericardiocentesis was performed successfully. There was an initial drainage of around 500 mL. Protamine sulfate was administered and ACT was subsequently 177 seconds; however, bleeding continued and a further 600 mL was drained. The case was therefore discussed with the cardiothoracic surgical team and the hematologist. The decision was made to give 4-factor PCC in the form of Beriplex (CSL Behring GmbH, Marburg, Germany). Within 10 minutes, it was noted that there was a significant reduction in the volume of blood being drained. The patient was transferred to the cardiac intensive care unit, remaining intubated and ventilated overnight.

Minimal further drainage was noted during the night, and echocardiography the following morning confirmed trivial remaining pericardial effusion and no signs of tamponade. The patient was successfully extubated at day 1. Repeat imaging at day 3 showed there was trivial pericardial effusion and the drain was removed. Following drain removal the patient recovered well on the coronary care unit. Edoxaban 60 mg once a day was recommenced a few days following discharge, with no further adverse effects noted.

Discussion

This case describes the successful use of PCC in the management of significant bleeding in the context of a procedural complication and edoxaban therapy. There is limited evidence that suggests that PCC might be useful as a reversal agent during significant bleeding events in patients on DOACs. Three small trials have looked at rivaroxaban, apixaban, and dabigatran in healthy subjects, with variable results, and there is a small amount of clinical data. Data on PCC use with edoxaban therapy is limited to small trials in healthy subjects and animal models, but no clinical data has previously been reported.

Evidence for the reversal of rivaroxaban, apixaban, and dabigatran include small trials in healthy volunteers measuring the effects of PCC on various clotting parameters. PCC reversed anticoagulation using rivaroxaban and apixaban but was not effective in reversing the effects of dabigatran.[7–9] Clinical data exist on the effects of PCC on the outcomes of patients with spontaneous and traumatic intracranial bleeding and other traumatic injury in the context of rivaroxaban and apixaban, with some success in reducing hemorrhagic complications and hematoma expansion.[10,11]

With regard to edoxaban, a phase 1 double-blind, randomized, placebo-controlled study was conducted in 110 healthy subjects who had undergone a punch biopsy while on edoxaban 60 mg and then given 1 of 3 doses of PCC. They demonstrated a dose-dependent reversal of bleeding duration and endogenous thrombin potential with complete reversal at 50 IU/kg of PCC. There was partial reversal of prothrombin time and bleeding volume. They concluded that PCC was safe, well tolerated, and potentially useful in the reversal of edoxaban anticoagulation.[12]

In another phase 1 placebo-controlled trial, 24 healthy subjects aged 18–45 were randomized to 2 cohorts, 1 given edoxaban 60 mg and the other edoxaban 180 mg. Both were then followed 1 hour later by PCC 25 IU/kg, PCC 50 IU/kg, or placebo. Thrombin generation parameters were reversed maximally by PCC 50 IU/kg but with a high degree of variability, and prothrombin time was not reversed. All treatments were tolerated well. The authors advised caution in interpreting these results owing to the high variability seen.[13]

In a rabbit model of bleeding in the context of edoxaban therapy, animals were randomized to 3 groups: control with no edoxaban plus saline, edoxaban plus saline, and edoxaban plus 4-factor PCC 50 IU/kg ($n = 11$ in each group). Animals underwent a standardized kidney incision and were monitored for hemostasis and coagulation parameters. Blood loss, time to hemostasis, prothrombin time, whole blood clotting time, and endogenous thrombin potential were all significantly improved by 4-factor PCC. They concluded that PCC significantly decreased hemorrhage associated with edoxaban.[14]

The prothrombotic effects of PCC should be considered. Modern PCC formulations have been shown to have a low occurrence of thromboembolic complications. One review of 506 cases reversing warfarin using PCC reported a thromboembolic risk of 1.4%, including stroke, deep vein

thrombosis, and myocardial infarction.[15] Another analysis on the use of PCC in different clinical situations suggested an incidence of thromboembolism of 0.9%.[5] These complications may have related to underlying thrombotic risk factors. In the case we have reported, no ablation was performed; however, if ablation lesions had been delivered in the left atrium this may have created an additional dilemma between life-threatening bleeding and thromboembolic complication.

Bleeding may have been exacerbated by intravenous heparin given during the procedure, as well as DOAC anticoagulation. Our policy is to administer an initial heparin dose of 100 units/kg in the context of uninterrupted DOAC anticoagulation before transseptal puncture. ACT is then measured every 15 minutes, aiming for readings greater than 300 seconds, with further heparin boluses as required. If bleeding occurs, protamine sulfate is administered to reverse the effects of heparin. It is reasonable to suspect that heparin reversal in this case may have increased the chance of hemostasis. However, it was interesting to note that a further 600 mL of blood was drained despite normalization of ACT following protamine administration but within 10 minutes of PCC administration bleeding slowed rapidly. It is therefore important to consider timely reversal of both heparin and DOAC anticoagulation if AF ablation is complicated by life-threatening bleeding.

Conclusion

We report on the first successful clinical use of PCC in the treatment of a patient who suffered life-threatening pericardial bleeding complicating an AF ablation procedure while on edoxaban. Significant bleeding in the initial stages was seen to reduce quickly after the administration of PCC and the patient recovered well. This adds to growing evidence that PCC may be effective in cases of severe bleeding in the context of DOAC therapy.

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